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Application of Proline-Functionalised 1,2-Diphenylethane-1,2-Diamine (DPEN) in Asymmetric Transfer Hydrogenation of Ketones.

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Keywords: Asymmetric catalysis • Transfer hydrogenation • Ruthenium • Peptides

A series of enantiomerically-pure ligands containing a combination of proline and DPEN groups have been prepared and employed in the asymmetric transfer hydrogenation of ketones. In the case of cyclic ketones, alcohols with *ees* of up to 96 % were obtained.

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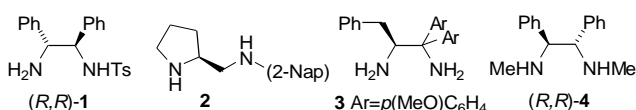
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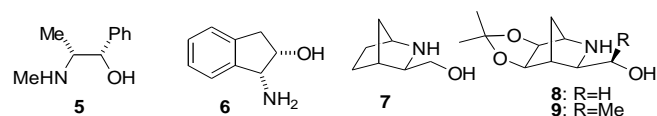
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Introduction

Asymmetric transfer hydrogenation (ATH) is a mild and versatile method for the enantioselective reduction of C=O and C=N bonds.^[1] Suitable catalysts for this reaction are typically complexes of homochiral ligands with Ru, Ir and Rh, whilst either *i*PrOH or formic acid/triethylamine (FA:TEA, 5:2 azeotrope)^[2] is normally used as the hydrogen donor. The reduction may also be carried out in aqueous solution using sodium formate as the hydrogen source.

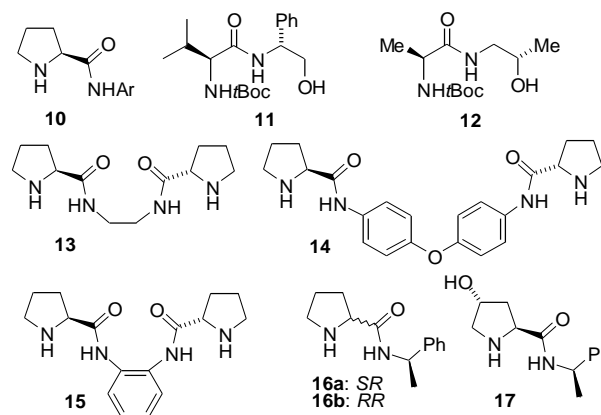


A number of ligands have been developed for use in organometallic ATH reactions, which include diamines such as TsDPEN **1**,^[3] **2**,^[4a-c] **3**,^[4d] and **4**.^[5] Complexes of β -amino alcohols^[6-8] such as **5-9** are capable of reducing ketones with high enantioselectivities when used with *i*PrOH as the hydrogen donor. Ligands include **6**⁷ and the 2-azanorboronyl methanols **8** and **9**.^[8] In case of ligands **1-9**, an 18-electron complex is formed with a TM salt, complemented by an η^6 -arene ring, and this is the active complex which enters the catalytic cycle.^[1]



In 1998, Furukawa et al reported the use of proline, and other amino acids, as ligands for the ATH of acetophenone in *i*PrOH; enantiomeric excesses of up to 82 % were reported.^[9] Several other reports have since reported the use of amino acids^[10,11] and their

amide derivatives.^[12-15] Chung *et al* described the use of complexes of N-aryl prolinamides **10** with [Ru(II)(arene)Cl]₂.^[12] Through variation of the N-aryl group, and the η^6 -arene, a system capable of reduction of acetophenone derivatives in up to 98.8 % *ee* was identified. Prolinamide also works effectively as a ligand with Ru(II) or Rh(III) in ATH of ketones with isopropanol as the hydrogen source.^[14]

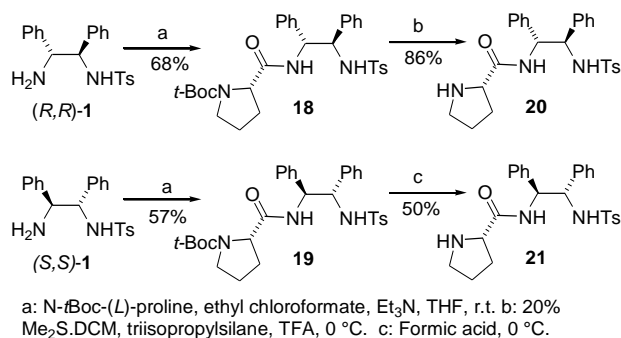


Adolfsson *et al.* have reported a series of amino acid-derived ligands containing proximal alcohol groups, typified by **11** and **12**, for ketone ATH.^[16] It was found that the configuration of the product was controlled most strongly by the chirality of the stereocentre in the *t*Boc-protected amino acid portion of the ligand. The reduction was demonstrated to involve the participation of Li cations in bridging the ketone substrate to the Ru-bound alkoxy group.^[16g,h,i] The reversal of reduction enantioselectivity could be achieved using thioamides of the amino acids.^[16e,i,j] The ATH of ketones in water^[17] has been the subject of a number of studies.^[18,19] In 2004 Xiao^[20] found that the use of a ruthenium (*p*-cymene) TsDPEN catalyst ((S,S) -**1**) in water exhibited good catalytic activity when using sodium formate as the hydrogen donor.^[21,22] The pH of the reaction had a pivotal effect; at low pH, the nitrogen atom adjacent to the tosyl group protonates and becomes detached from the metal centre, thus reducing activity, whilst at higher pH the ligand-metal bonding remains intact. Several water-soluble TsDPEN-derived ligands containing sulfonic acids^[23,24] have been evaluated.

Prolinamide derivatives were first employed for ketone ATH in water in 2001; reduction products of up to 95.3 % ee were generated^[25] and in some cases, surfactants could be used to improve activity.^[26] Multisubstrate screening methods, where several substrates can be screened simultaneously, have been described using prolinamide catalysts.^[27,28] Dimeric ligands **13** – **15**,^[29] when complexed to Ru(II), were capable of reducing acetophenone in water, using sodium formate as the hydrogen donor at 40 °C. Increasing the rigidity of the diamine spacer i.e. in **14** and **15** improved the enantioselectivity of the catalyst and reduction products of 56 % and 66 % e.e. respectively were formed. Ligands **16** and **17**, developed by Mao,^[30] are also capable of reducing acetophenone under the same conditions, with comparable enantioselectivity. Alteration of the proline chirality in ligands **16** produced a reversal in the stereochemistry of reduction.

Results and Discussion

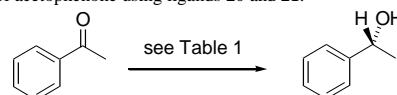
Given the literature precedent, and our ongoing interest in the development of catalysts for ATH reactions, we investigated ligands containing a combination of a 1,2-diamine function and a proline group. The reaction of each enantiomer of TsDPEN **1** with a protected *S*-proline derivative was achieved using ethylchloroformate in the coupling reaction. Removal of the *t*Boc group from **18** and **19** required the use of different reagents to obtain products **20** and **21** (Scheme 1).



Scheme 1. Synthesis of compounds **20** and **21** from the coupling of the two enantiomers of **1** and proline.

Compound **21** has been applied to an aldol reaction of ketones with 1,2-diketones,^[31] whilst very similar compounds (SO₂Ph in place of Ts) have been prepared via ring opening of a sulfonated aziridine ring and applied to the organocatalysis of aldol reactions.^[32] Several derivatives of C2-symmetric DPEN and of *trans* 1,2-diaminocyclohexane, bearing the combination of prolinamide and carbamate/thiocarbamate,^[33-37] or dialkyl substituents,^[38] have been reported in organocatalytic asymmetric transformations. We first attempted acetophenone reduction using **20** and **21** with a 5:2 mixture of FA/TEA as the solvent and hydrogen donor (Table 1). Unfortunately under these conditions, as well as the alternative conditions of *i*PrOH as the solvent/hydrogen donor, no reduction was achieved. However, the use of sodium formate in water resulted in successful reduction, giving 1-phenylethanol in 90 % e.e. and 22 % conversion after 24 hours at 40 °C with **20**, and complete reduction at 80 °C with either ligand, although amide **20** was marginally more active. The ability to achieve highly enantioselective reductions under such mildly basic conditions provides an advantage in some cases, e.g. when base-sensitive substrates are employed.

Table 1: ATH of acetophenone using ligands **20** and **21**.^[a]



Entry	Ligand	Temp	Conditions ^a	Conv. (%) ^[b]	e.e. (%) ^[b]	<i>R/S</i> . ^[c]
1	20	40	Aq. HCO ₂ Na	22	90	<i>R</i>
2	20	40	FA/TEA	0	-	-
3	20	40	Isopropanol	0	-	-
4	20	40	FA/TEA ^[d]	0	-	-
5	20	60	Aq. HCO ₂ Na	100	90	<i>R</i>
6	20	80	Aq. HCO ₂ Na	100	79	<i>R</i>
7	21	60	Aq. HCO ₂ Na	83	83	<i>R</i>
8	21	80	Aq. HCO ₂ Na	100	83	<i>R</i>

[a] Conditions; Aq. HCO₂Na: **20/21** (0.02 mmol, 1 mol-%), [RuCl₂(*p*-cymene)]₂ (0.01 mmol, 1 mol-% by Ru), HCO₂Na (10 mmol), H₂O (6 cm³), acetophenone (2 mmol), 40 °C; Formic acid / triethylamine: **20**, (0.02 mmol, 2 mol-%), [RuCl₂(*p*-cymene)]₂ (0.01 mmol, 2 mol-% by Ru), formic acid / triethylamine (5:2) 0.5 cm³, acetophenone (1 mmol); Isopropanol: **20**, (0.02 mmol, 2 mol-%), [RuCl₂(*p*-cymene)]₂ (0.01 mmol, 2 mol-% by Ru), isopropanol (4 cm³), acetophenone (1 mmol). [b] Determined by G.C. [c] Determined by comparison of G.C. and optical rotation with literature data. [d] Catalytic species formed in water and transferred to FA/TEA system.

An attempt was made to form a catalyst in water and then transfer it to the formic acid system. After stirring ligand **20** and [RuCl₂(*p*-cymene)]₂ for 1 hour in water at 40 °C, the mixture was extracted with ethyl acetate and the solvent removed under reduced pressure to leave an orange solid. Analysis of the mass spectrum of this solid showed the masses of the expected complexes with ion distributions that matched the predicted patterns for the 18 electron ([Ru(cymene)**20**.Cl]; *m/z* 734.18 for the ¹⁰²Ru³⁵Cl isotope) and the dechlorinated ([Ru(cymene)**20**-H]; *m/z* 698.20 for the ¹⁰²Ru isotope) species of the desired complex (see supporting information). This solid was then used under the 5:2 FA/TEA reaction conditions, but once again showed no reactivity under these conditions (Table 1, Entry 4).

The reduction of a further series of ketones was investigated (Table 2). When the ligands were tested on the cyclic ketone 1-tetralone, the enantiomeric selectivity of the two catalysts proved to be almost the same. Although, once again, the (*S,S*)-TsDPEN containing catalyst proved to be more active.

Determination of the configuration of the major products revealed that the proline chirality dominates the enantioselectivity of the catalyst, with the TsDPEN chirality having a smaller, but not insignificant, effect. The proline-TsDPEN ligands were also tested in Ir and Ir Cp* complexes (Table 3); their reaction rates and selectivities were reduced compared to the ruthenium metal complexes. Interestingly, with Rh, the TsDPEN chirality dominates the reduction enantioselectivity. This may indicate that the metal centre is bound to different sites on the ligand when Rh is used compared to Ru and Ir.

Table 2. Transfer hydrogenation of ketones by ruthenium complexes of ligands **20** and **21** in water.^[a]

$\text{R}^1-\text{C}(=\text{O})-\text{R}^2 \xrightarrow[\text{NaHCO}_2, \text{H}_2\text{O}, 60^\circ\text{C}, 24\text{ h}]{[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2, \text{ligand}} \text{R}^1-\text{CH}(\text{OH})-\text{R}^2$						
Entry	Lig- and	R ¹	R ²	Conv. (%) ^[b]	e.e. (%) ^[b]	R/S ^[c]
1	20	Ph	Me	100	90	<i>R</i>
2	21	Ph	Me	100	83	<i>R</i>
3	20	<i>c</i> C ₆ H ₁₁	Me	25	0	-
4	21	<i>c</i> C ₆ H ₁₁	Me	40	0	-
5	20	<i>p</i> (MeO)C ₆ H ₄	Me	76	86	<i>R</i>
6	21	<i>p</i> (MeO)C ₆ H ₄	Me	92	57	<i>R</i>
7	20	<i>o</i> (MeO)C ₆ H ₄	Me	54	74	<i>R</i>
8	21	<i>o</i> (MeO)C ₆ H ₄	Me	95	65	<i>R</i>
9	20	2,4-(MeO) ₂ C ₆ H ₃	Me	11	51	<i>R</i>
10	20	<i>p</i> (Cl)C ₆ H ₄	Me	90	88	<i>R</i>
11	21	<i>p</i> (Cl)C ₆ H ₄	Me	100	71	<i>R</i>
12	20	<i>o</i> (Cl)C ₆ H ₄	Me	100	85	<i>R</i>
13	21	<i>o</i> (Cl)C ₆ H ₄	Me	100	64	<i>R</i>
14	20	Ph	Et	66	84	<i>R</i>
15	21	Ph	Et	84	78	<i>R</i>
16	20	Ph	<i>c</i> C ₆ H ₁₁	6	32	<i>R</i>
17	21	Ph	<i>c</i> C ₆ H ₁₁	6	57	<i>R</i>
18	20	α -tetralone		8	77	<i>R</i>
19	21	α -tetralone		45	78	<i>R</i>

[a] Conditions: [RuCl₂(p-cymene)]₂ (0.5 mol-%, equivalent to 1 mol-% metal centre), proline-TsDPEN ligand (1 mol-%), ketone substrate (2 mmol), sodium formate (10 mmol), water (6 cm³), 60 °C. [b] Determined by G.C. [c] Determined by comparison of G.C. and optical rotation with literature data.

Coordination of ligands **20** and **21** can occur at three sites on the ligand, the secondary amine, the amide and the sulphonamide. Ligands **20**, **21** and **16/17**^[21] give the same major product enantiomer. As ligands **16** and **17** only contain two of the possible coordination sites, it is likely that the catalytic complex formed using ligands **20** and **21** predominantly coordinate through these two sites to give the same major product. Arrangement of the ligands with ruthenium in this pocket can give a complex (Figure 1a) that would form the observed major (*R*) alcohol in a similar manner to the established concerted mechanism for arene/Ru/TsDPEN complexes (Figure 1b).^[1]

Our interest next turned to ligands containing two prolinamides, i.e. **22** and **23**, linked by a DPEN spacer. As was the case for **20** and **21**, these have been used previously as catalysts for aldol reactions,^[31,39,40] and as a ligands for the addition of cyano groups to ketones.^[41] Bisprolinamides bridged by 1,2-diamino aryl rings have also been employed in aldol reactions.^[42] The coupling of two *t*Boc protected prolines to each enantiomer of DPEN was followed by removal of the *t*Boc groups using 20 % Me₂S.DCM, triisopropyl silane and trifluoroacetic acid method to form ligands **22** and **23** respectively (Scheme 2).

Table 3. Transfer hydrogenation of ketones by Ir and Rh complexes of ligands **20** and **21** in water.^[a]

$ \begin{array}{ccc} \text{R}^1-\text{C}(=\text{O})-\text{R}^2 & \xrightarrow[\text{NaHCO}_2, \text{H}_2\text{O}, 60^\circ\text{C}, 24\text{ h}]{[\text{Ir}(\text{C}_5\text{Me}_5)_2\text{Cl}_2]_2 \text{ or } [\text{Rh}(\text{C}_5\text{Me}_5)_2\text{Cl}_2]_2, \text{ligand}} & \text{R}^1-\text{CH}(\text{OH})-\text{R}^2 \end{array} $							
Entry	Me- tal	Lig- and	R ¹	R ²	Conv. (%) ^[b]	e.e. (%) ^[b]	R/S ^[c]
1	Ir	20	Ph	Me	9	47	<i>R</i>
2	Ir	21	Ph	Me	0	-	-
3	Ir	20	<i>p</i> (MeO)C ₆ H ₄	Me	5	38	<i>R</i>
4	Ir	20	<i>p</i> (Cl)C ₆ H ₄	Me	33	29	<i>R</i>
5	Ir	21	<i>p</i> (Cl)C ₆ H ₄	Me	33	14	<i>R</i>
6	Rh	20	Ph	Me	13	84	<i>R</i>
7	Rh	21	Ph	Me	21	67	<i>S</i>
8	Rh	20	cC ₆ H ₁₁	Me	22	0	-
9	Rh	21	cC ₆ H ₁₁	Me	28	0	-
10	Rh	20	<i>p</i> (MeO)C ₆ H ₄	Me	3	63	<i>R</i>
11	Rh	21	<i>p</i> (MeO)C ₆ H ₄	Me	7	52	<i>S</i>
12	Rh	20	<i>p</i> (Cl)C ₆ H ₄	Me	21	83	<i>R</i>
13	Rh	21	<i>p</i> (Cl)C ₆ H ₄	Me	68	85	<i>S</i>
14	Rh	20	<i>o</i> (Cl)C ₆ H ₄	Me	41	59	<i>R</i>
15	Rh	21	<i>o</i> (Cl)C ₆ H ₄	Me	37	50	<i>S</i>
16	Rh	20	Ph	Et	10	28	<i>R</i>
17	Rh	21	Ph	Et	7	22	<i>S</i>

[a] Conditions: [IrCl₂(Cp*)]₂ (0.5 mol-%, equivalent to 1 mol-% metal centre), proline-TsDPEN ligand (1 mol-%), ketone substrate (2 mmol), sodium formate (10 mmol), water (6 cm³), 60 °C. [b] Determined by G.C. [c] Determined by comparison of G.C. and optical rotation with literature data.

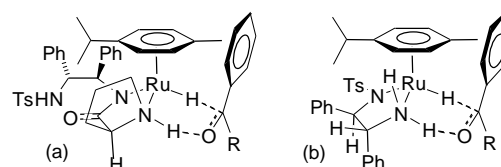
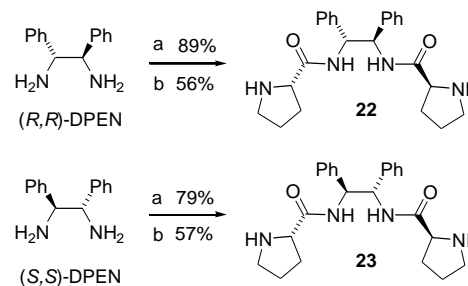


Figure 1. Proposed structures of the Ru(II)/arene complexes of (a) ligand **20** and (b) (*R,R*)-TsDPEN **1**^[1] that would give the *R*-configuration alcohol product following the concerted mechanism for ATH in water. The position of the substituents on the η⁶-arene ring is arbitrary.



a: N-*t*Boc-(L)-proline, ethyl chloroformate, Et₃N, THF, r.t.
b: 20% Me₂S.DCM, triisopropylsilane, TFA, 0 °C.

Scheme 2. Synthesis of compounds **22** and **23** through the coupling of the two enantiomers of DPEN and two proline molecules.

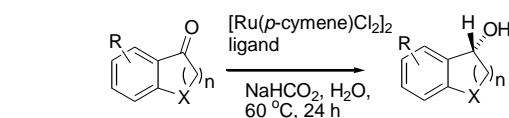
Initial testing into the use of the diproline/DPEN ligands followed the same conditions as previously established, including the relative equivalents of ruthenium metal to ligand (Table 4). Ligands **22** and **23** were found to be less selective than ligands **20** and **21** for the hydrogenation of acyclic ketones, although they showed a similar level of activity. The exception to this is the hydrogenation of cyclohexyl methyl ketone to 1-cyclohexylethan-1-ol, which led to a racemic mixture when reduced with **20** and **21**. When **22** and **23** were tested on the bicyclic ketone 1-tetralone, 1-tetralol was formed with very high ee and at comparable reaction rates to ligands **20** and **21** (Table 5). The hydrogenation of 1-indanone showed the same pattern with regards to both enantiomeric selectivity and catalytic activity. The more enantioselective ligand **23** was tested with other bicyclic ketones, varying both the size of the alkyl cyclic ring and the substituents on both the alkyl and aromatic rings (Table 5). These results revealed that an $[\text{RuCl}_2(p\text{-cymene})\text{23}]$ complex is able to catalyse the reduction of bicyclic aryl ketones with moderate to good conversions and good to excellent enantioselectivity. Reactions with low conversions can be improved by increasing catalyst loading (Table 5, Entry 3), or increasing reaction time (Table 5, Entry 4), with little degradation in enantioselectivity.

Table 4. Transfer hydrogenation of ketones by ruthenium complexes of ligands **22** and **23** in water.^[a]

Entry	Ligand	R ¹	R ²	Conv. (%) ^[b]	e.e. (%) ^[b]	R/S ^[c]
1	22	Ph	Me	99	86	<i>R</i>
2	23	Ph	Me	100	83	<i>R</i>
3	22 ^[d]	Ph	Me	11	12	<i>R</i>
4	23 ^[d]	Ph	Me	13	24	<i>R</i>
5	22	<i>c</i> C ₆ H ₁₁	Me	54	68	<i>R</i>
6	23	<i>c</i> C ₆ H ₁₁	Me	22	66	<i>R</i>
7	22	<i>p</i> (MeO)C ₆ H ₄	Me	63	83	<i>R</i>
8	23	<i>p</i> (MeO)C ₆ H ₄	Me	90	77	<i>R</i>
9	22	<i>o</i> (MeO)C ₆ H ₄	Me	66	65	<i>R</i>
10	23	<i>o</i> (MeO)C ₆ H ₄	Me	98	53	<i>R</i>
11	22	<i>p</i> (Cl)C ₆ H ₄	Me	100	87	<i>R</i>
12	23	<i>p</i> (Cl)C ₆ H ₄	Me	98	79	<i>R</i>
13	22	<i>o</i> (Cl)C ₆ H ₄	Me	99	80	<i>R</i>
14	23	<i>o</i> (Cl)C ₆ H ₄	Me	99	66	<i>R</i>
15	22	Ph	Et	82	86	<i>R</i>
16	23	Ph	Et	90	80	<i>R</i>
17	22	Ph	<i>c</i> C ₆ H ₁₁	82	86	<i>R</i>
18	23	Ph	<i>c</i> C ₆ H ₁₁	90	80	<i>R</i>
19	23	Ph	CH ₂ Cl	100	81	<i>R</i>

[a] Conditions: $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.5 mol-%, equivalent to 1 mol-% metal centre), diproline-DPEN ligand (1 mol-%), ketone substrate (2 mmol), sodium formate (10 mmol), water (6 cm³), 60 °C. [b] Determined by G.C. [c] Determined by comparison of G.C. and optical rotation with literature data. [d] $[\text{RhCl}_2(\text{Cp}^*)]_2$ used instead of $[\text{RuCl}_2(p\text{-cymene})]_2$

Table 5. Transfer hydrogenation of commercially available bicyclic ketones by ruthenium complexes of ligands **22** and **23** in water.^[a]



Entry	Ligand	X	n	R	Conv. (%) ^[b]	e.e. (%) ^[c]	R/S ^[d]
1	22	CH ₂	2	H	14	75	<i>R</i>
2	23	CH ₂	2	H	48	98	<i>R</i>
3	22 ^[e]	CH ₂	2	H	98	95	<i>R</i>
4	23 ^[f]	CH ₂	2	H	78	98	<i>R</i>
5	22	CH ₂	1	H	99	71	<i>R</i>
6	23	CH ₂	1	H	100	91	<i>R</i>
7	23	CH ₂	3	H	61	89	<i>R</i>
8	23	CH ₂	1	7-Me	43	89	<i>R</i> ^[g]
9	23	CH ₂	2	6-OMe	13	85	<i>R</i>
10	23	CH ₂	2	Furan ^[h]	33	85 ^[i]	<i>R</i>
11	23	O	2	H	100	96 ^[i]	<i>R</i>
12	23	S	2	H	100	92	<i>R</i>
13	23	O	2	6-Cl	12	86	<i>R</i>

[a] Conditions: $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.5 mol-%, equivalent to 1 mol-% metal centre), diproline-DPEN ligand (1 mol-%), ketone substrate (2 mmol), sodium formate (10 mmol), water (6 cm³), 60 °C. [b] Determined by G.C. [c] Determined by G.C. unless shown. [d] Determined by comparison of G.C. and optical rotation with literature data. [e] 2 mol-% catalyst used. [f] Reaction time 48 h. [g] Configuration inferred from results of other ketones. [h] Furan ring in place of phenyl in substrate. [i] Determined by HPLC.

Adding an oxygen or sulfur atom to the 4 position on the tetralone alkyl ring does not reduce the rate of the hydrogenation of the substrate and does little to change the enantioselectivity of the catalyst (Table 5, Entries 11 and 12). Altering the aryl ring however, causes a decrease in both reaction rate and enantioselectivity, most significantly when a substituent is positioned on the 6 position of the tetralone. Ligand **13**^[29] is similar to ligands **22** and **23**, differing in that the latter have two additional chiral centres on the ethyl linker. The chirality of the major product alcohol (*R*) formed using all of these ligands is the same, being determined by the chirality of the proline portion of the ligand.

With the Noyori TsDPEN complex system the reduction of cyclohexyl methyl ketone provides an indication of the differences in reduction of aryl-alkyl ketones and dialkyl ketones. In the aryl-alkyl ketone the stereochemistry of the product is directed through a π -face interaction between the aromatic group on the substrate and the aryl group on the complex (Figure 1).^[1] With dialkyl ketones this interaction cannot occur and the interaction is due to steric interactions between the largest alkyl group and the η^6 -arene ring on the complex. For this reason the reduction product of a dialkyl ketone of lower or opposite stereochemistry is often observed. In the reduction of cyclohexyl methyl ketone by complexes containing ligands **20** or **21**, a racemic mixture was formed. This indicates that the steric interactions between the substrate and both the η^6 -arene ring on the metal centre and the ligand could be similar, resulting in no preference between the two possible transition states. For the reduction using ligand **22** or **23**, the product was non-racemic, however, the stereochemistry of the cyclohexyl methyl ketone is the same as that for reduction of aryl-alkyl ketones. This suggests that the cyclohexyl methyl ketone and

the aryl-alkyl ketones adopt the same orientation in the reduction step. This would indicate that the ligand in the diproline-DPEN (**22** and **23**) complexes may have a larger effective steric bulk than the η^6 -arene ring in the context of the reduction reactions.

Ligands **22** and **23** have four coordination sites, therefore it is possible to coordinate two metal centres to each ligand forming a diruthenium complex. To test the effect of altering the metal : ligand ratio, acetophenone reduction was performed using half the amount of ligand **22** relative to ruthenium dimer. This creates a 2:1 ratio of metal to dimer, compared to the 1:1 ratio using the original conditions. The conversions obtained from samples taken at different times indicated that the reaction with a 2:1 ratio of metal to ligand proceeded at a slower rate than the reaction with a 1:1 ratio (Table 6). The e.e. of the (*R*)-phenylethanol product of the two reactions is the same and remains constant as the reaction proceeds, hence the catalytic complex formed in the two reactions appears to be the same. The reduced rate of the 2:1 metal to ligand ratio indicates that there is less available catalytic complex in this reaction and that the catalytic complex contains one metal centre per ligand. This could be due to steric hindrance around the coordination sites, allowing only one metal to bind..

Table 6. The effect of altering the ratio between ligand and metal for the transfer hydrogenation of acetophenone in water.^[a]

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1-\text{C}-\text{R}^2 \end{array} \xrightarrow[\text{NaHCO}_2, \text{H}_2\text{O}, 60^\circ\text{C}, 24\text{ h}]{\begin{array}{c} [\text{Ru}(p\text{-cymene})\text{Cl}_2]_2 \\ \text{ligand} \end{array}} \begin{array}{c} \text{H} \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{R}^1-\text{C}-\text{R}^2 \end{array} $		
Time (h)	2:1 Metal : Ligand	1:1 Metal : Ligand
	Conversion (%) ^[b]	Conversion (%) ^[b]
6	52	89
12	79	95
24	92	99
e.e. (%) ^[b]	83	83

[a] Conditions: $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.5 mol-%, equivalent to 1 mol-% metal centre), **22** (1 mol-% (1:1) or 0.5 mol-% (2:1)), acetophenone (2 mmol), sodium formate (10 mmol), water (6 cm³), 60 °C. [b] Determined by G.C.

Conclusions

Four ligands have been developed for the asymmetric transfer hydrogenations of ketones. These ligands show a good level of activity when the reaction is performed in water with sodium formate as the hydrogen donor. Ligands **20** and **21** were the most successful of the four in the reduction of acyclic ketones, reducing ketones with up to full conversion and 90 % e.e. in 24 hours. The stereochemistry of the major product was predominantly determined by the stereochemistry of the proline ring, but the 1,2-diphenyl-1,2-diamine has an effect, possibly due to interactions between the aryl rings of the ligand and the substrate. For the reduction of bicyclic ketones ligands, **22** and **23** proved to be more effective. Complexes containing ligand **23** proved to be both more stereoselective than complexes containing ligand **22** and were also more active. The catalytic complex appears to contain the metal centre and the ligand in a 1 to 1 ratio.

Experimental Section

(Unless otherwise stated, all reactions were performed in oven dried glassware and under an atmosphere of argon. Room temperature refers to ambient room temperature (20 – 22 °C), 0 °C refers to an ice slush bath and -78 °C refers to a dry ice acetone bath. Heated experiments were conducted using thermostatically controlled oil baths or Asynt aluminium heating blocks. NMR spectra were run on either a Bruker DPX-300 (300 MHz) or a Bruker DPX-400 (400 MHz). All NMR δ values are in ppm and all *J* values are in Hz. Low resolution mass spectrometry was run on a Bruker Esquire2000 electrospray mass spectrometer. High resolution mass spectrometry was run on Bruker MicroTOF. Melting points were obtained using a Stuart Scientific Melting Point SMP1 and are uncorrected. Infrared spectroscopy was run on a PerkinElmer Spectrum 100. Optical rotation was obtained from an Optical Activity Ltd. AA-1000 Polarimeter. GC was run on either a Hewlett Packard 5890 gas chromatograph linked to a Hewlett Packard HP3396A integrator or a Perkin Elmer 8500 chromatograph linked to a PC running DataApex Clarity software. HPLC was run on chromatograph consisting of a Gilson 305 Piston Pump, a Gilson 805 Manometric Module, a Gilson 811B Dynamic Mixer and a Gilson 115 Variable Wavelength Detector linked to a Hewlett Packard 3396 Series II integrator.

(*S*)-tert-Butyl-2-(((1*R*,2*R*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)-carbamoyl)pyrrolidine-1-carboxylate (18**):** *N*-*t*Boc-(*L*)-proline (1.0 g, 4.7 mmol) and triethylamine (2.1 cm³, 14.1 mmol) were dissolved in anhydrous THF (23.5 cm³) and cooled to 0 °C. Ethyl chloroformate (0.47 cm³, 5.0 mmol) was added and the mixture was stirred at 0 °C for 30 minutes. (*R,R*)-1,2-Diphenylethylene-1,2-diamine **1** (1.7 g, 4.7 mmol) was added and the reaction was stirred at room temperature overnight. The THF was removed under reduced pressure and ethyl acetate and water were added. The organic layer was washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure to leave the product **18** as a white solid. (1.8 g, 3.2 mmol, 68 %). mp 187 – 192 °C. $[\alpha]_D^{25} -34.0$ (c 1.0 in CHCl₃). $\nu_{\text{max}}/\text{cm}^{-1}$ 2975 (w), 1652 (s), 1521 (m), 1496 (m), 1456 (m), 1385 (s), 1366 (s), 1324 (s), 1253 (w), 1154 (s), 1120 (s), 1089 (s), 1028 (w), 919 (m), 853 (w), 810 (m), 771 (m), 730 (m) and 697 (s). ¹H NMR (300 MHz, CDCl₃, Me₄Si): δ = 1.14 (3H, br s, -C(CH₃)₃ rotamer), 1.54 (6H, br s, -C(CH₃)₃ rotamer), 1.89 – 1.96 (m, 1H, -CHH-), 2.12 – 2.14 (m, 1H, -CHH-), 2.25 (s, 3H, -CH₃), 2.33 – 2.46 (m, 1H, -CHH-), 3.35 – 3.59 (m, 1H, -CHH-), 3.66 (dd, ³*J*_{HH} = 2.3, ³*J*_{HH} = 7.8 Hz, 1H, -C(O)CH-), 4.20 – 4.37 (m, 2H, -NCH₂-), 5.28 (br s, 1H, -C(O)NHCH-), 6.54 (br s, 1H, -S(O)₂NHCH-), 6.81 (d, ³*J*_{HH} = 7.5 Hz, 2H, Ar-H), 6.88 – 7.01 (m, 7H, Ar-H), 7.12 – 7.15 (m, 3H, Ar-H) and 7.37 (d, ³*J*_{HH} = 7.5 Hz, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ = 20.7, 23.8, 27.4, 30.7, 46.7, 57.5, 59.8, 61.4, 62.2, 79.8, 126.1, 126.6, 126.9, 127.1, 127.3, 127.8, 128.3, 137.1, 137.5, 137.7, 141.8, 154.6 and 172.9. *m/z* (ESI⁺) 586 ([M + Na], 100 %). HRMS calcd for C₃₁H₃₇N₃O₅Sn 586.2346, found 586.2348 (0.3 ppm error).

(*S*)-N-(((1*R*,2*R*)-2-(4-Methylphenylsulfonamido)-1,2-diphenylethyl)pyrrolidine-2-carboxamide (20**):** (*S*)-*tert*-butyl-2-(((1*R*,2*R*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate **18** (355 mg, 0.63 mmol) was dissolved in 20 % Me₂S-DCM complex (9.3 cm³). Triisopropylsilane (0.18 cm³, 0.78 mmol) was added and the mixture cooled to 0 °C. Trifluoroacetic acid (8.7 cm³, 113.6 mmol) was added dropwise at 0 °C and the mixture was allowed to slowly warm to room temperature and was stirred overnight. The reaction was quenched at 0 °C with the addition of saturated aqueous potassium carbonate and the majority of the dimethyl sulfide was removed under reduced pressure. Water was added and the product was extracted with DCM (2 x 30 cm³). The combined organic extracts were combined, dried over magnesium sulfate and the organic solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The crude product was

dissolved in hot ethyl acetate and hexane was added until the product precipitated out of solution. The pure product **20** was filtered off as a white solid. (251 mg, 0.54 mmol, 86 %). mp 100 – 102 °C. $[\alpha]_D^{31}$ -17.6 (c 1.0 in CHCl₃). $\nu_{\max}/\text{cm}^{-1}$ 3299 (w), 2870 (w), 1643 (s), 1600 (w), 1497 (s), 1456 (m), 1325 (s), 1203 (m), 1156 (s), 1089 (s), 1029 (w), 921 (m), 807 (s), 772 (m), 756 (m), 698 (s) and 668 (s). ¹H NMR (300 MHz, CDCl₃, Me₄Si): δ = 1.69 – 1.82 (m, -CH₂-2H), 1.89 – 2.02 (m, 1H, -CHH-), 2.09 – 2.22 (m, 3H, -CHH-, -CH₂NHCH- and -C(O)CH-), 2.26 (s, -3H, CH₃), 3.07 (ddd, ³J_{H,H} = 2.3, ³J_{H,H} = 6.6, ³J_{H,H} = 6.6 Hz, 2H, -NHCH₂-), 3.79 (dd, ³J_{H,H} = 5.6, ³J_{H,H} = 8.9 Hz, 1H, -C(O)NHCH(Ph)CH-), 4.66 (d, ³J_{H,H} = 10.1 Hz, 1H, -S(O)₂NHCH-), 5.12 (dd, ³J_{H,H} = 8.9, ³J_{H,H} = 10.1 Hz, 1H, -S(O)₂NHCH(Ph)CH-), 6.79 (d, ³J_{H,H} = 8.3 Hz, 2H, Ar-H), 6.89 – 6.98 (m, 5H, Ar-H), 7.00 – 7.03 (m, 2H, Ar-H), 7.16 – 7.18 (m, 3H, Ar-H), 7.34 (d, ³J_{H,H} = 8.3 Hz, 2H, Ar-H) and 8.62 (d, ³J_{H,H} = 5.6 Hz, 1H, -C(O)NH-). ¹³C NMR (75 MHz, CDCl₃): δ = 20.7, 25.6, 30.1, 46.7, 57.7, 59.8, 63.5, 126.1, 126.6, 126.9, 127.2, 127.9, 128.3, 128.6, 130.4, 137.2, 137.4, 137.5, 141.8 and 175.6. *m/z* (ESI⁺) 464 ([M + H], 100 %). HRMS calcd for C₂₆H₃₀N₃O₃S 464.2002, found 464.2011 (1.8 ppm error).

(S)-tert-Butyl-2-(((1*S*,2*S*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)-carbamoyl)pyrrolidine-1-carboxylate (19): *N*-*t*Boc-(*L*)-proline (500 mg, 2.33 mmol) and triethylamine (1.1 cm³) were dissolved in anhydrous THF (11.7 cm³) and cooled to 0 °C. Ethyl chloroformate (0.24 cm³, 2.5 mmol) was added and the mixture was stirred at 0 °C for 30 minutes. (*R,R*)-1,2-Diphenylethylene-1,2-diamine **1** (850 mg, 2.32 mmol) was added and the reaction was stirred at room temperature overnight. The THF was removed under reduced pressure and ethyl acetate and water were added. The organic layer was washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure to leave the product **19** as a white solid. (743 mg, 1.32 mmol, 57 %). mp 102 – 106 °C. $[\alpha]_D^{32}$ -17.1 (c 1.0 in CHCl₃). $\nu_{\max}/\text{cm}^{-1}$ 3351 (w), 3196 (w), 2975 (w), 1695 (s), 1666 (s), 1600 (w), 1543 (m), 1496 (m), 1478 (w), 1456 (m), 1393 (s), 1366 (s), 1324 (m), 1289 (m), 1245 (m), 1209 (w), 1155 (s), 1121 (s), 1089 (s), 1070 (m), 1029 (w), 927 (m), 887 (w), 853 (w), 812 (m), 770 (m), 759 (m), 697 (s) and 667 (s). ¹H NMR (400 MHz, CDCl₃, Me₄Si): δ = 1.32 (s, 9H, -C(CH₃)₃), 1.84 – 1.89 (m, 3H, -CH₂- and -CHH-), 2.30 (s, 3H, -CH₃), 2.46 (br s, 1H, -S(O)₂NH-), 3.22 – 3.33 (m, 2H, -CH₂-), 3.42 – 3.48 (m, 1H, -C(O)CH-), 4.25 (d, ³J_{H,H} = 8.8 Hz, 1H, -C(O)NHCH-), 4.62 (d, ³J_{H,H} = 8.8 Hz, 1H, -S(O)₂NHCH-), 5.03 – 5.20 (m, 1H, -NCHH-), 6.31 (br s, 1H, -NCHH-), 6.82 (d, ³J_{H,H} = 7.2 Hz, 2H, Ar-H), 6.95 – 7.03 (m, 7H, Ar-H), 7.12 (br m, 3H, Ar-H), 7.44 (d, ³J_{H,H} = 7.2 Hz, 2H, Ar-H) and 8.23 (br s, 1H, -C(O)NHCH-). *m/z* (ESI⁺) 586 ([M + Na], 100 %). HRMS calcd for C₃₁H₃₇N₃O₅Na 586.2346, found 586.2353 (1.1 ppm error).

(S)-N-(((1*S*,2*S*)-2-(4-Methylphenylsulfonamido)-1,2-diphenylethyl)pyrrolidine-2-carboxamide (21):^[30] To (*S*)-tert-Butyl-2-(((1*S*,2*S*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate **19** (150 mg, 0.266 mmol) was added formic acid (1.1 cm³) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 12 hours. The formic acid was then removed under reduced pressure to leave a white solid, which was neutralised by the addition of aqueous ammonia. The product was extracted with DCM and the combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to leave the product **21** as a white solid (61 mg, 0.132 mmol, 50 %). mp 97 – 100 °C. $[\alpha]_D^{32}$ -0.7 (c 0.5 in CHCl₃). $\nu_{\max}/\text{cm}^{-1}$ 3063 (w), 3031 (w), 2873 (w), 1647 (s), 1600 (w), 1511 (s), 1495 (m), 1455 (m), 1322 (s), 1203 (w), 1184 (w), 1153 (s), 1089 (s), 1071 (m), 1029 (m), 934 (m), 811 (m), 756 (m), 697 (s) and 666 (s). ¹H NMR (400 MHz, CDCl₃, Me₄Si): δ = 1.52 – 1.65 (m, 2H, -CH₂-), 1.73 – 1.80 (m, 1H, -CHH-), 2.06 – 2.13 (m, 2H, -CHH- and C(O)CH-), 2.18 (s, 3H, -CH₃), 2.82 – 2.88 (m, 1H, -NHCHH-), 2.91 – 2.97 (m, 1H, -NHCHH-), 3.85 (dd, 1H, ³J_{H,H} = 8.2, ³J_{H,H} = 9.7 Hz, -C(O)NHCH(Ph)CH-), 4.53 (d, ³J_{H,H} = 9.7 Hz, 1H, -S(O)₂NHCH-), 5.12 (dd,

1H, ³J_{H,H} = 9.7, ³J_{H,H} = 9.7 Hz, -S(O)₂NHCH(Ph)CH-), 6.78 – 6.92 (m, 10H, Ar-H), 7.07 (m, 2H, Ar-H), 7.33 (d, ³J_{H,H} = 7.9 Hz, 2H, Ar-H) and 8.58 (d, ³J_{H,H} = 8.2 Hz, 1H, -C(O)NH-). ¹³C NMR (75 MHz, CDCl₃): δ = 21.3, 26.0, 30.5, 47.1, 58.7, 60.5, 63.9, 126.7, 127.2, 127.5, 127.6, 127.7, 127.9, 128.4, 129.0, 138.1, 138.4, 138.5, 142.3 and 176.0. *m/z* (ESI⁺) 464.2 ([M + H], 100 %). HRMS calcd for C₂₆H₃₀N₃O₃S 464.2002, found 464.2000 (0.5 ppm error).

(S)-tert-Butyl-2-(((1*R*,2*R*)-2-((*S*)-1-(tert-butoxycarbonyl)pyrrolidine-5-carboxamido)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate: *N*-*t*Boc-(*L*)-proline (2.0 g, 9.3 mmol) and triethylamine (2 cm³) were dissolved in anhydrous THF (23.6 cm³) and cooled to 0 °C. Ethyl chloroformate (0.96 cm³, 10.0 mmol) was added and the mixture was stirred at 0 °C for 30 minutes. (*R,R*)-1,2-Diphenylethylene-1,2-diamine (1.2 g, 5.6 mmol) was added and the reaction was stirred at room temperature overnight. The THF was removed under reduced pressure and ethyl acetate and water were added. The organic layer was washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure to leave the product as a white solid. (2.5 g, 4.1 mmol, 89 %). mp 104 – 108 °C. $[\alpha]_D^{32}$ -98.7 (c 0.5 in CHCl₃). $\nu_{\max}/\text{cm}^{-1}$ 3338 (w), 2974 (w), 1695 (s), 1652 (s), 1520 (s), 1478 (m), 1454 (m), 1390 (s), 1365 (s), 1252 (m), 1159 (s), 1120 (m), 1087 (m), 1029 (w), 979 (w), 952 (w), 925 (w), 858 (w), 772 (m) and 698 (s). ¹H NMR (300 MHz, CDCl₃, Me₄Si): δ = 1.17 (br s, 9H, -C(CH₃)₃), 1.45 (br s, 9H, -C(CH₃)₃), 1.83 (br s, 6H, alkyl-H), 3.25 – 3.56 (br m, 4H, alkyl-H), 4.05 – 4.31 (br m, 4H, alkyl-H), 5.20 – 5.30 (br m, 2H, -CHCH-), 7.07 – 7.10 (m, 4H, Ar-H), 7.15 – 7.20 (m, 6H, Ar-H), 7.61 – 7.86 (m, 2H, 2 x -C(O)NH-). ¹³C NMR (75 MHz, CDCl₃): *m/z* (ESI⁺) 605 ([M – H], 24 %), 531 (93), 457 (100). HRMS calcd for C₃₄H₄₅N₄O₆ 605.3345, found 605.3314 (5.1 ppm error).

(S)-N-(((1*R*,2*R*)-1,2-Diphenyl-2-((*S*)-pyrrolidine-5-carboxamido)ethyl)pyrrolidine-2-carboxamide (22):^[31,39] (*S*)-tert-butyl-2-(((1*R*,2*R*)-2-((*S*)-1-(tert-butoxycarbonyl)pyrrolidine-5-carboxamido)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate (1.0 g, 1.7 mmol) was dissolved in 20 % Me₂S-DCM complex (21.3 cm³). Triisopropylsilane (0.8 cm³, 3.5 mmol) was added and the mixture cooled to 0 °C. Trifluoroacetic acid (20 cm³, 261 mmol) was added dropwise at 0 °C and the mixture was allowed to slowly warm to room temperature and was stirred overnight. The reaction was quenched at 0 °C with the addition of saturated aqueous potassium carbonate and the majority of the dimethyl sulfide was removed under reduced pressure. Water was added and the product was extracted with DCM (2 x 30 cm³). The combined organic extracts were combined, dried over magnesium sulfate and the organic solvent was removed under reduced pressure to leave the crude product **22** as a pale yellow solid. The crude product was dissolved in hot ethyl acetate and hexane was added until the product precipitated out of solution. The pure product was filtered off as a white solid. (384 mg, 0.94 mmol, 56 %). mp 140 – 144 °C. $[\alpha]_D^{32}$ -39.8 (c 0.4 in CHCl₃). $\nu_{\max}/\text{cm}^{-1}$ 3290 (m), 3062 (w), 2948 (w), 2874 (w), 1646 (s), 1516 (s), 1495 (s), 1455 (m), 1418 (m), 1290 (m), 1253 (m), 1201 (s), 1131 (m), 1030 (m), 1002 (w), 915 (w), 834 (m), 800 (m), 755 (m), 697 (s). ¹H NMR (300 MHz, CDCl₃, Me₄Si): δ = 1.66 – 1.77 (m, 4H, alkyl-H), 1.79 – 1.90 (m, 2H, alkyl-H), 2.08 – 2.20 (m, 2H, alkyl-H), 2.38 (br s, 2H, -NHCH(Ph)CH(Ph)NH-), 2.90 – 3.05 (m, 4H, 2 x -CH₂NH-), 3.69 (dd, 2H, ³J_{H,H} = 5.5, ³J_{H,H} = 9.0 Hz, 2 x -CH₂NHCH-), 5.21 (dd, ³J_{H,H} = 2.5, ³J_{H,H} = 5.5 Hz, 2H, 2 x -C(O)CH-), 7.06 – 7.09 (m, 4H, Ar-H), 7.14 – 7.21 (m, 6H, Ar-H) and 8.40 (br s, 2H, 2 x -C(O)NH-). ¹³C NMR (75 MHz, CDCl₃): δ = 25.4, 31.0, 46.5, 57.7, 58.3, 126.8, 126.9, 127.9, 138.3 and 173.7. *m/z* (ESI⁺) 407.2 [M + H] (100 %). HRMS (ESI⁺) calc for C₂₄H₃₁N₄O₂ 407.2442, found 407.2449 (1.8 ppm error).^[39]

(S)-tert-Butyl-2-(((1*S*,2*S*)-2-((*S*)-1-(tert-butoxycarbonyl)pyrrolidine-5-carboxamido)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate: *N*-*t*Boc-(*L*)-proline (2 g, 9.4 mmol) and triethylamine (2 cm³) were

dissolved in anhydrous THF (23.6 cm³) and cooled to 0 °C. Ethyl chloroformate (0.96 cm³, 10.0 mmol) was added and the mixture was stirred at 0 °C for 30 minutes. (*R,R*)-1,2-Diphenylethylene-1,2-diamine (1.2 g, 5.6 mmol) was added and the reaction was stirred at room temperature overnight. The THF was removed under reduced pressure and ethyl acetate and water were added. The organic layer was washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure to leave the product as a white solid. (2.5 g, 4.1 mmol, 89 %). mp 118 – 123 °C. [α]_D²⁸ -28.7 (c 0.2 in CHCl₃). ν_{max} /cm⁻¹ 3320 (w), 2977 (w), 2879 (w), 1689 (s), 1661 (s), 1526 (m), 1496 (m), 1479 (w), 1455 (w), 1398 (s), 1365 (s), 1283 (s), 1240 (m), 1208 (w), 1160 (s), 1121 (m), 1089 (w), 1030 (w), 984 (w), 924 (w), 887 (w), 860 (w), 771 (m) and 698 (s). ¹H NMR (300 MHz, CDCl₃, Me₄Si): δ = 1.34 (br s, 18H, 2 x -C(CH₃)₃), 1.77 – 1.90 (m, 6H, 3 x alkyl-H), 2.27 – 2.53 (m, 2H, alkyl-H), 3.16 – 3.35 (br m, 2H, alkyl-H), 3.35 – 3.61 (m, 2H, alkyl-H), 4.28 – 4.41 (br m, 2H, alkyl-H), 5.11 – 5.14 (m, 2H, -CHCH-), 6.98 – 7.09 (br m, 4H, Ar-H), 7.09 – 7.18 (br m, 6H, Ar-H), 8.05 (br s, 1H, -C(O)NH-) and 8.44 (br s, 1H, -C(O)NH-). *m/z* (ESI⁺) 605 ([M – H], 47 %), 531 (100), 457 (57). HRMS calcd for C₃₄H₄₅N₄O₆ 605.3345, found 605.3322 (3.7 ppm error).

(*S*)-N-((*IS*,2*S*)-1,2-Diphenyl-2-((*S*)-pyrrolidine-5-carboxamido)ethyl)pyrrolidine-2-carboxamide (23**):**^[39,40] (*S*)-*tert*-Butyl-2-(((*IS*,2*S*)-2-((*S*)-1-(*tert*-butoxycarbonyl)-pyrrolidine-5-carboxamido)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate (500 mg, 0.83 mmol) was dissolved in 20 % Me₂S-DCM complex (10.6 cm³). Triisopropylsilane (0.4 cm³, 1.7 mmol) was added and the mixture cooled to 0 °C. Trifluoroacetic acid (10 cm³, 131 mmol) was added dropwise at 0 °C and the mixture was allowed to slowly warm to room temperature and was stirred overnight. The reaction was quenched at 0 °C with the addition of saturated aqueous potassium carbonate and the majority of the dimethyl sulfide was removed under reduced pressure. Water was added and the product was extracted with DCM (2 x 30 cm³). The combined organic extracts were combined, dried over magnesium sulfate and the organic solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The crude product was dissolved in hot ethyl acetate and hexane was added until the product precipitated out of solution. The pure product **23** was filtered off as a white solid. (104 mg, 0.26 mmol, 31 %). mp 114 – 118 °C. [α]_D²⁶ +7.3 (c 1.0 in CHCl₃). ν_{max} /cm⁻¹ 3296 (m), 3033 (w), 2951 (w), 2870 (w), 1645 (s), 1513 (s), 1455 (m), 1255 (m), 1201 (m), 1103 (m), 1030 (m), 915 (m), 841 (m), 755 (m) and 697 (s). ¹H NMR (300 MHz, CDCl₃, Me₄Si): δ = 1.52 – 1.68 (4H, m 2 x -CH₂-), 1.68 – 1.81 (m, 2H, 2 x -CHH-), 2.01 – 2.13 (m, 2H, 2 x -CHH-), 2.55 (br s, 2H, -NHCH(Ph)CH(Ph)NH-), 2.81 – 2.89 (m, 2H, 2 x -NHCHH-), 2.94 – 3.02 (m, 2H, 2 x -NHCHH-), 3.74 (dd, ³J_{H,H} = 6.3, ³J_{H,H} = 8.8 Hz, 2H, 2 x -CH₂NHCH-), 5.19 (dd, ³J_{H,H} = 2.3, ³J_{H,H} = 6.3 Hz, 2H, 2 x -C(O)CH-), 7.05 – 7.08 (m, 4H, Ar-H), 7.15 – 7.18 (m, 6H, Ar-H) and 8.51 (br s, 2H, 2 x -C(O)NH-). ¹³C NMR (75 MHz, CDCl₃): δ =, 25.9, 30.5, 47.1, 58.7, 61.5, 127.4, 127.7, 128.5, 138.8 and 175.0. *m/z* (ESI⁺) 407.3 [M + H], 429.2 [M + Na]. HRMS (ESI⁺) calcd for C₂₄H₃₁N₄O₂ 407.2442, found 407.2444 (0.5 ppm error):^[39,40]

General procedure for the racemic reduction of ketones: The ketone (2 mmol) was dissolved in methanol (1 cm³) and DCM (1 cm³) and sodium borohydride (49 mg, 1.3 mmol) was added in portions and the reaction was stirred at room temperature for 1 hour. The solvents were removed under reduced pressure and water was added. The product was extracted with DCM and the organic extracts were combined, dried over magnesium sulfate and the solvent removed under reduced pressure to leave the racemic alcohol, which was purified by column chromatography if necessary.

General procedure for asymmetric transfer hydrogenation: Ligand (0.02 mmol) and ruthenium-dichloro-*p*-cymene dimer (6.1 mg, 0.01 mmol) were dissolved in water (6 cm³) and the mixture was stirred at 60 °C for 1 hour. The ketone (2 mmol) and sodium formate (1.04 g, 10 mmol) were added and the mixture stirred at 60 °C for 24 hours. The reaction was then allowed to cool to room temperature and the product extracted with ethyl acetate. The organic layer was filtered through a plug of silica and the solvent removed under reduced pressure to leave the product which was purified by column chromatography if necessary. Characterisation data and ee determination methods for reduction products^[43-50] are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Characterisation data for ketone reduction products and copies of NMR, GC and HPLC data.

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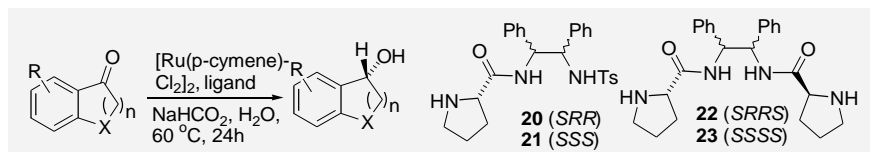
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Layout 2:



Ligands **20-23** were prepared and used for the asymmetric transfer hydrogenation of a range of ketones. Using ligand **23**, bicyclic ketones were reduced in up to 96 % ee.

Asymmetric transfer hydrogenation

Charles V. Manville, Gordon Docherty, Ranbir Padda and Martin Wills* . Page No. – Page No.

Application of Proline-Functionalised 1,2-Diphenylethane-1,2-Diamine (DPEN) in Asymmetric Transfer Hydrogenation of Ketones.

Keywords: Asymmetric catalysis / Transfer hydrogenation / Ruthenium / Peptides.

